

AMENDMENTS TO THE SPECIFICATION

Please replace the Abstract of the Disclosure, beginning at page 37, line 3, with the following rewritten paragraph.

A method and apparatus for use in determining the cardiac output. The method includes ~~quantitatively measuring the patient's airflow, a first parameter indicative of the percent oxygen inhaled and exhaled by the patient's oxygen uptake,~~ and a second parameter indicative of the patient's fractional arterial oxygen concentration. The method also includes inducing a change in the patient's arterial oxygen concentration while taking these measurements to monitor the effects of the change in the patient's arterial oxygen concentration. The cardiac output is determined from the data collected regarding the effects of the change in the patient's arterial oxygen concentration.

After the title and before the section entitled "BACKGROUND OF THE INVENTION" insert the following new section heading and paragraph.

--CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 120 as a Continuation of U.S. Patent Appln. No. 10/172,271 filed June 14, 2002, which claims priority under 35 U.S.C. § 120 as a Continuation of U.S. Patent Appln. No. 09/691,595 filed October 18, 2000, now U.S. Patent No. 6,413,226, which claims priority from provisional U.S. Patent Appln. No. 60/369,708 filed April 3, 2002, the contents of which are incorporated herein by reference.--

Please replace the paragraph beginning at page 1, line 10, with the following rewritten paragraph.

There are several generally accepted techniques for measuring cardiac output (CO), which is the total volumetric flow of blood through the heart, and, thus, through the body at any given time. These techniques include: thermodilution, dye dilution, the direct Fick method, and partial CO₂ rebreathing. Thermodilution involves injecting cold saline directly into the right atrium of the heart and measuring the temperature change downstream in the pulmonary artery using a temperature sensor placed in this artery. Cardiac output is determined based on this temperature change versus time. Dye dilution is similar to thermodilution except that a dye, rather than cold saline, is injected into the ~~art~~pulmonary artery. The amount of dye collected downstream is measured to determine the patient's cardiac output.

Please replace the paragraph beginning at page 3, line 15, with the following rewritten paragraph.

This partial CO₂ rebreathing technique, however, has several disadvantages. Namely, the patient is preferably intubated or breathing through a trachea tube when taking the flow and CO₂ measurements to capture the total volume of CO₂. In addition, the patient must be heavily sedated or unconscious so that he or she is not breathing spontaneously. If the patient is breathing spontaneously, the increased CO₂ level in the blood during the rebreathing phase would automatically trigger the patient's respiratory system to speed up or deepen the breaths to remove the excess CO₂. It is well known that for most patient's, the level of CO₂ is not as important as the level of O₂, and is as a the mechanism for triggering ventilation. Such a change in rate or depth of rapid or deep breathing prevents an accurate determination of cardiac output under this technique. It should also be noted that the use of end tidal CO₂, as opposed to the arterial CO₂ content, may introduce errors in determining cardiac output, because there are situations where the end tidal CO₂ may not correlate with the arterial CO₂ content. The partial CO₂ rebreathing

cardiac output measurement technique is also disadvantageous because it does not adequately account for shunt blood flow, which is blood that is not oxygenated during the respiratory cycle. This flow cannot be directly measured, but must be estimated when using this conventional cardiac output measurement technique.

Please replace the paragraph beginning at page 4, line 11, with the following rewritten paragraph.

Accordingly, it is an object of the present invention to provide a method of measuring cardiac output that overcomes the shortcomings of conventional cardiac output measurement techniques. This object is achieved according to one embodiment of the present invention by providing a cardiac output measurement method that includes quantitatively measuring a patient's airflow, a first parameter indicative of a percent oxygen inhaled and exhaled by the patient's oxygen uptake, and a second parameter indicative of the patient's fractional arterial oxygen concentration. The present method also includes inducing a change in the patient's arterial oxygen concentration and repeating these measurements to monitor the effects resulting from inducing the change in the patient's arterial oxygen concentration. The patient's cardiac output is determined based on the data collected.

Please replace the paragraph beginning at page 5, line 1, with the following rewritten paragraph.

It is yet another object of the present invention to provide an apparatus for non-invasively determining the cardiac output of a patient, including a spontaneously breathing patient, that does not suffer from the disadvantages associated with conventional cardiac measurement systems. This object is achieved by providing an apparatus that includes a patient

~~flow measuring system capable of quantitatively measuring a patient's airflow, i.e., the flow of gas to and from a patient, an oxygen analyzing system adapted to measure~~system for measuring a
~~first parameter indicative of a percent oxygen inhaled and exhaled by such a patient's oxygen~~
~~uptake,~~ and means for measuring a second parameter indicative of the patient's fractional arterial oxygen concentration, such as a pulse oximeter. A processor determines the cardiac output based on the ~~measured patient airflow, the first parameter, and the second parameter.~~ In addition, an output device outputs the result indicative of the patient's cardiac output.

Please replace the paragraph beginning at page 6, line 4, with the following rewritten paragraph.

Figs. 3A and 3B are graphs ~~is a graph~~ illustrating the change in oxygen uptake that takes place during an induced change in arterial oxygen concentration according to the cardiac output measurement method of the present invention;

Please replace the paragraph beginning at page 6, line 9, with the following rewritten paragraph.

Figs. 5A and 5B ~~and 6~~ are graphs illustrating the change in oxygen uptake and arterial oxygen concentration, respectively, resulting from the induced change in arterial oxygen concentration including the potential effects of recirculation;

Fig. 6 is a graph illustrating the change in arterial oxygen concentration resulting from the induced change in arterial oxygen concentration including the potential effects of recirculation;

Please replace the paragraph beginning at page 7, line 13, with the following rewritten paragraph.

(1) quantitatively measuring (a) ~~the patient's airflow, (b)~~ a parameter indicative of the percent oxygen inhaled and exhaled by oxygen uptake of the patient, and ~~(be)~~ a parameter indicative of the patient's fractional arterial oxygen concentration (XaO_2);

Please replace the paragraph beginning at page 7, line 16, with the following rewritten paragraph.

(2) inducing a change in the patient's arterial oxygen concentration while taking measurements (a) ~~(c)~~ and (b) set forth in step (1) to monitor the effects of the change in the patient's arterial oxygen concentration; and

Please replace the paragraph beginning at page 8, line 4, with the following rewritten paragraph.

It is important to note that the patient's arterial oxygen concentration, not their carbon dioxide concentration, is what is being manipulated in order to induce a change in the patient's oxygen uptake and fractional arterial oxygen concentration. As a result, this method can be performed on a spontaneously breathing patient, as well as on a patient who is not spontaneously breathing. Unlike changing the patient's CO_2 concentration, changing the patient's arterial O_2 concentration for a short time will not cause the patient to automatically attempt to alter their breathing pattern to move the O_2 concentration back to normal. Because this cardiac output measurement technique involves inducing a change in the patient's arterial

oxygen concentration, it is referred to as an oxygen concentration modification cardiac output measurement method.

Please replace the paragraph beginning at page 9, line 3, with the following rewritten paragraph.

According to the present invention, the patient's quantitative airflow and a parameter indicative of the percent oxygen inhaled and exhaled by the patient are measured to determine the patient's oxygen uptake. Oxygen uptake, also referred to as oxygen consumed by the patient, is the amount of oxygen absorbed into the blood in the lungs. It is typically expressed in liters as a volume $\dot{V}O_2$ or in liters per minute (lpm) as a volume flow rate $\dot{V}O_2$. Thus, equation (1) can be rewritten as follows:

$$CO(\text{liters}) = \frac{\Delta \dot{V}O_2}{\Delta X_{aO_2}(T)} , \text{ or as} \quad (2)$$

where T is a period over which the arterial oxygen concentration changes in response to a change in oxygen absorbed into the blood, as discussed in greater detail below with reference to Fig. 4.
Equation (1) can also be rewritten as:

$$CO(\text{lpm}) = \frac{\Delta \dot{V}O_2}{\Delta X_{aO_2}} . \quad (3)$$

Please replace the paragraph beginning at page 10, line 14, with the following rewritten paragraph.

There are a variety of parameters indicative of fractional arterial oxygen concentration, X_{aO_2} , of a patient that can be measured and used in the cardiac output

determination method. One embodiment of the present invention contemplates measuring at least one of the following blood gas constituents, SaO_2 , PaO_2 , and CaO_2 as the parameter indicative of the patient's fractional arterial oxygen concentration XaO_2 . These parameters are measured from an arterial blood sample or using a continuously indwelling catheter. It is preferable for one or more of these constituents to be measured continuously, for example, using an indwelling catheter so that the effects of the induced change in arterial oxygen concentration on the oxygen uptake and fractional arterial oxygen concentration can be monitored on a substantially continuous basis. This is especially important because of the relatively short duration of the effects of the induced change in arterial oxygen concentration resulting from the oxygen concentration modification step.

Please replace the paragraph beginning at page 13, line 15, with the following rewritten paragraph.

A patient's SaO_2 , PaO_2 , or CaO_2 can only be measured by sampling the patient's arterial blood or using a continuously indwelling catheter, either of which is a relatively invasive procedure. SpO_2 , on the other hand, which is an estimation of SaO_2 , is measured non-invasively. Therefore, measuring the patient's SpO_2 has the advantage of being fast, easy, and non-invasive. If SpO_2 is taken as the measured parameter, it is considered an approximation of SaO_2 , i.e., $\text{SpO}_2 \approx \text{SaO}_2$. Thus, the conversion factor k is applied to the measured SpO_2 to arrive at the patient's fractional arterial oxygen concentration XaO_2 , i.e., $\text{XaO}_2 \approx \text{SpO}_2 * k$.

Please replace the paragraph beginning at page 14, line 17, with the following rewritten paragraph.

Reducing the patient's oxygen saturation can be accomplished by reducing the fraction of inspired oxygen (FIO₂) in the patient's inhaled gas. This can be accomplished, for example, by increasing the concentration of other inhaled gas constituents, such as nitrogen, which has the effect of lowering the patient's arterial oxygen saturation. In one embodiment of the present invention, the patient breathes nitrogen for one or more breaths, thereby reducing their arterial oxygen concentration. This technique is particularly suited for patients with a relatively high baseline oxygen concentration.

Please replace the paragraphs beginning at page 16, line 13; page 17, line 4; and page 17, line 9 , with the following rewritten paragraphs.

It is well known that the rate of flow (Q) of a fluid, which is typically expressed in liters per minute (lpm), is defined as:

$$Q = \frac{V}{t}, \quad (12)$$

where V is volume and t is time. For a given period of time, t_a to t_b, the rate of flow of fluid during that period is determined as follows:

$$Q = \frac{V}{t_b - t_a} \quad (13)$$

The following relationships are also known:

$$XaO_2 = \frac{VO_2}{V}, \text{ or} \quad (14)$$

$$V = \frac{VO_2}{XaO_2} \quad (15)$$

Substituting equation (14) into equation (13) yields:

$$Q = \frac{VO_2}{XaO_2 * (t_b - t_a)} \quad (16)$$

Equation (16), however, cannot be used to determine a patient's cardiac output because it does not take into consideration the fact that in the pulmonary system, the venous blood contains a predetermined level of oxygen before it is oxygenated in the lungs. In addition, this equation does not take into consideration blood that is shunted across the lungs and does not get oxygenated during a breathing cycle.

The present invention takes these items into consideration and accounts for their effect by, in essence, determining the baseline oxygen concentration and oxygen uptake for the patient, then executing the oxygen concentration modification step, in which the patient's fractional arterial oxygen concentration is changed from the baseline value. The present invention determines cardiac output by monitoring the arterial oxygen concentration and oxygen uptake during this oxygen concentration modification step and by comparing the changes in the arterial oxygen concentration and oxygen uptake to the baseline levels.

It is well known that the flow of fluid in a stream or conduit can be measured by monitoring a known mass or bolus of an indicator fluid downstream of where it was introduced into that stream. For example, it is known that the flow of fluid can be expressed as follows:

$$\text{Flow} = \frac{m}{cT} = \frac{\text{mass of indicator injected}}{\text{concentration of indicator} \times \text{time period of change in concentration}} \quad (12)$$

This relation is described, for example, by L. A. Geddes et al. in the textbook entitled, "Principles of Applied Biomedical Instrumentation", 3rd Edition, 1989, pages 576-578, and is the same principle used to measure cardiac output using the dye dilution technique.

The present invention contemplates introducing a bolus of non-oxygen into a patient's circulatory system as the indicator fluid rather than introducing a conventional dye. In other words, the present invention contemplates perturbing the cardio-respiratory system by removing a known volume of oxygen, which is referred to herein as introducing a bolus of non-oxygen into the system. Introducing a bolus of non-oxygen is equivalent to inducing a change in the patient's arterial oxygen concentration as discussed above. If the indicator fluid is a bolus or mass of non-oxygenated blood, the relationship described in equation (12) can be rewritten as follows:

$$\text{CO} = \frac{\text{VO}_{2(\text{bolus})}}{(\bar{X}_a \text{O}_2)(T)} \quad (13)$$

where CO is cardiac output, $\text{VO}_{2(\text{bolus})}$ is the volume of non-oxygen taken up or absorbed by the blood in the lungs, i.e., the oxygen uptake of the non-oxygen bolus. T is the period over which the arterial oxygen concentration changes, i.e., a decrease in the illustrated embodiment, in response to the change in oxygen taken up by the patient (See Fig. 4), which is also a decrease in the illustrated embodiment. Finally, $\bar{X}_a \text{O}_2$ is the mean arterial oxygen concentration over period T.

Please replace the paragraph beginning at page 17, line 17, with the following rewritten paragraph.

Figs. 3A and 3B ~~is are~~ are graphs that illustrates the change in a patient's volume flow rate of oxygen taken in by the blood $\dot{V}\text{O}_2$ (Fig. 3A) and the change in oxygen uptake, VO_2 (Fig. 3B) that takes place during the oxygen concentration modification step, in which a change in the arterial oxygen concentration, XaO_2 , is induced using any of the above-described techniques. More specifically, Figs. 3A and 3B illustrates the change in oxygen uptake that takes place by having the patient take one breath, i.e., from time t_1 to t_3 , that is relatively devoid of oxygen. It should be noted that the change in oxygen uptake volume is illustrated in a step fashion in Fig. 3B because oxygen uptake is measured and calculated on a breath-by-breath basis. As shown in Figs. 3A and 3B, it takes several breaths for the patient's oxygen uptake to stabilize back to its baseline level. Area A in Fig. 3A represents the change in the oxygen uptake ΔVO_2 $\Delta\dot{V}\text{O}_2$ of the patient that occurs as a result of the oxygen concentration modification step. Similarly, Fig. 3B represents a histogram of the oxygen uptake volumes 100, 102, 104, and 106 resulting from the oxygen modification step.

Please replace the paragraph beginning at page 18, line 7, with the following rewritten paragraphs.

Fig. 4 illustrates the change in arterial oxygen saturation concentration $\bar{S}_aO_2 - \bar{X}_aO_2$ resulting from the induced change in arterial oxygen concentration, which, in this embodiment, involves having the patient take one breath that is devoid of oxygen. In other words, Fig. 4 graphically shows the decrease in arterial oxygen concentration that occurs over time period T resulting from the oxygen concentration modification step shown in Figs. 3A and 3B, which, in the present embodiment, is a decrease in the oxygen uptake.

The volume of non-oxygen taken by the patient's blood, $VO_{2(bolus)}$, which is shown as area A in Fig. 3A, can be calculated as follows:

$$VO_{2(bolus)} = \int_0^T [\dot{V}O_{2(baseline)}(0) - \dot{V}O_{2(bolus)}(t)] dt, \quad (14)$$

where $\dot{V}O_{2(baseline)}(0)$ is the baseline steady-state volume flow rate of oxygen taken up by the blood prior to the bolus injection, and $\dot{V}O_{2(bolus)}(t)$ is the volume flow rate of oxygen taken up by the blood after the bolus injection. It should be noted that period T in equation (14) can be the same as period T in Fig. 4, or it can be a different period, so long as the function of calculating the volume of non-oxygen taken up by the blood is substantially met, i.e., area A is calculated to a close approximation.

The mean arterial oxygen concentration, \bar{X}_aO_2 , which is shown in Fig. 4, can be calculated as follows:

$$\bar{X}_aO_2 = \frac{1}{T} \int_0^T [X_aO_2(0) - X_aO_2(t)] dt, \quad (15)$$

where $X_aO_2(0)$ is the baseline steady-state arterial oxygen concentration prior to the bolus injection, and $X_aO_2(t)$ is the arterial oxygen concentration after the bolus injection.

Combining equations (14) and (15) into equation (13) yields:

$$CO = \frac{\int_0^T [\dot{V}O_{2(baseline)}(0) - \dot{V}O_{2(bolus)}(t)] dt}{\int_0^T [X_aO_2(0) - X_aO_2(t)] dt} \quad (16)$$

Thus, a patient's cardiac output can be estimated by monitoring the patient's oxygen uptake using any conventional technique and by measuring a parameter indicative of the patient's fractional arterial oxygen concentration (X_aO_2) before and after a bolus of non-oxygen is introduced into the patient's system, which has the effect of altering the patient's arterial oxygen concentration.

It can be appreciated that the expression $\dot{V}O_{2(baseline)}(0) - \dot{V}O_{2(bolus)}(t)$ in the numerator in equation (16) represents the change in the volume flow rate of oxygen taken up by the blood relative to the baseline steady-state volume flow rate. In the example shown in Figs. 3A and 3B, this change is shown as a lowering of the volume flow rate of consumed oxygen, i.e., dipping of the $\dot{V}O_{2(bolus)}(t)$ curve below the baseline, because in this example, the patient was presented with a bolus of non-oxygen, e.g., by reducing the FIO_2 .

However, the present invention also contemplates presenting the patient with a bolus of increased oxygen, e.g., by increasing the FIO_2 . The result will be an increase in the volume flow rate of consumed oxygen, i.e., an increase of the $\dot{V}O_{2(bolus)}(t)$ curve above the baseline. In which case, the change in the volume flow rate of oxygen taken by the blood relative to the baseline steady-state volume flow rate in equation (16) can be expressed as follows:

$$\dot{V}O_{2(bolus)} = \int_0^T [\dot{V}O_{2(bolus)}(t) - \dot{V}O_{2(baseline)}(0)] dt \quad (17)$$

This would similarly cause the change in arterial oxygen concentration to appear as an increase over the baseline value so that equation (16) can be expressed as:

$$\overline{X_a O_2} = \frac{1}{T} \int_0^T [X_a O_2(t) - X_a O_2(0)] dt, \quad (18)$$

Thus, as before, we can substitute equations (17) and (18) into equation (13) to get:

$$CO = \frac{\int_0^T [\dot{V}O_{2(bolus)}(t) - \dot{V}O_{2(baseline)}(0)] dt}{\int_0^T [X_a O_2(t) - X_a O_2(0)] dt}, \quad (19)$$

Equation (19) represents situations where the patient receives an increased level of oxygen as a means to alter the arterial oxygen concentration. It should be noted, however, that equation (16) is suitable for either situation, because the signs in the numerator and denominator would cancel where there is an increase over the baseline value.

It can be further appreciated that the numerator in equation (13) represents by the sum of the volumes $\dot{V}O_2$ in the histogram shown in Fig. 3B. That is, summing volumes indicated by levels 100, 102, 104, and 106 yields an indication of the total volume of non-oxygen taken in by the blood. Thus, equation (13) can be rewritten as:

$$CO = \frac{\sum_0^T \Delta \dot{V}O_2}{\overline{X_a O_2} * T}, \quad (20)$$

where $\sum_0^T \Delta \dot{V}O_2$ represents the sum of the bars of the histogram during period T (which is determined as discussed above with respect to Fig. 4). Substituting equation (15) into equation (20) allows equation (20) to be rewritten as:

$$CO = \frac{\sum_0^T \Delta \dot{V}O_2}{\int_0^T [X_a O_2(0) - X_a O_2(t)] dt}, \quad (21)$$

Either technique: 1) integrating curve $\dot{V}O_{2(bolus)}(t)$ over period T (Fig. 3A, equations (16) and (19)), or 2) summing the changes in volume of oxygen taken in by the blood ΔVO_2 over period T (Fig. 3B, equations (20) and (21)) provides an estimation of cardiac output.

Area B in Fig. 4 represents the change in arterial oxygen concentration ΔXaO_2 that occurs as a result of oxygen concentration modification step. These changes are measured and used to calculate cardiac output as follows:

$$Q = \frac{\Delta VO_2}{\Delta XaO_2 * (t_b - t_a)}, \quad (17)$$

where:

$$\Delta VO_2 = VO_{2 \text{ baseline}} - VO_{2 \text{ after oxygen concentration modification}} \quad (18)$$

$$\Delta XaO_2 = XaO_{2 \text{ baseline}} - XaO_{2 \text{ after oxygen concentration modification}} \quad (19)$$

Please cancel the paragraphs beginning at page 18, line 17, and page 19, line 4, in their entirety, as indicated below:

~~It can be appreciated from Figs. 3 and 4 that although the patient takes only one breath that is devoid of oxygen, the patient's oxygen uptake will shift from its baseline level for several breaths, i.e., from time t_a to time t_b . Therefore, the present invention contemplates summing the oxygen uptake that occurs for each breath over the entire time, t_a to t_b , that the oxygen uptake is shifted from baseline, which, in effect, amounts to determining the area A under the curve, which is why this technique is referred to in the section heading as "Calculating Cardiac Output Based on the Area Under the Curves."~~

~~The patient's arterial oxygen concentration will also shift from its baseline level for a period of time t_c to t_d . Therefore, the present invention contemplates finding the average arterial oxygen concentration resulting from the oxygen concentration modification step. It should be noted that the change in arterial oxygen concentration does not coincide with the start of the oxygen concentration modification step, i.e., $t_c \neq t_a$, because it takes some time for the change in inspired oxygen level to affect the patient's arterial oxygen concentration. Thus, equation (19) for the present invention is rewritten as:~~

$$Q = \frac{\sum \Delta VO_2}{\Delta \bar{X}aO_2 * (t_b - t_a)} \quad (20)$$

Equation (20) can be written in greater detail as:

$$Q = \frac{\sum (VO_{2 \text{ baseline}} - VO_{2 \text{ after oxygen concentration modification}})_{t_b - t_a}}{\int_c^d \left[\frac{SpO_{2 \text{ baseline}} - SpO_{2 \text{ after oxygen concentration modification}}}{(t_d - t_c)} \right] dt * (t_b - t_a)} \quad (21)$$

where:

$$VO_2 = \int_1^2 (Q_{\text{patient}} [\%O_2/100]) dt - \int_2^3 (Q_{\text{patient}} [\%O_2/100]) dt. \quad (22)$$

Please replace the paragraph beginning at page 19, line 17, with the following rewritten paragraphs.

Figs. 5A, 5B, and 6 are similar to Figs. 3A, 3B, and 4, respectively, except that Figs. 5A, 5B, and 6 take into consideration a scenario in which the bolus of oxygen or non-oxygen in the patient's blood begins to recirculate at time x during the oxygen concentration

modification step. As shown in Fig. 5A, recirculation will cause the volume flow rate of oxygen taken by the blood $\dot{V}O_{2(bolus)}(t)$, i.e., curve 103, to move toward the baseline level slower than if there was no recirculation, as indicated by portion 105 of curve 103. Similarly, as shown in Fig. 5B, the volume of oxygen taken in by the blood VO_2 will also move toward the baseline level more slowly. This can be appreciated by comparing Fig. 5A to 3A and Fig. 5B to Fig. 3B. As shown in Fig. 6, the arterial oxygen concentration XaO_2 curve 107 will also move toward the baseline, steady-state level more slowly than in the absence of recirculation.

The present invention contemplates dealing with the effects of recirculation by estimating time period T for use in the above cardiac output calculations. Estimating T involves extrapolating curve 107 using conventional extrapolation techniques, as shown by dashed line 109, to determine an extrapolated time t_a when the arterial oxygen concentration returns to the base line level. T is then determined from the start of the change in arterial oxygen concentration to time t_a , as shown in Fig. 6. This time period T based on extrapolation is then used, as shown in Fig. 5A to solve equation (15), or as shown in Fig. 5B to solve equation (19). For example, the consumed oxygen volumes corresponding to levels 110, 112, and 114 would be used in solving equation (19), while levels 116, 118, and 120 would not. It can be appreciated from Fig. 5, that the patient's oxygen uptake may increase above baseline and then eventually return to its baseline level at time t_{b1} . In this situation, the only area of interest is the area under the baseline, i.e., area A_1 . That is, the effects of recirculation, and, hence, area A_2 should be ignored in solving equation (21). For this reason, the present invention contemplates extrapolating to determine the baseline crossing point, which corresponds to point t_b in equation (21). Thus, the change in oxygen uptake resulting from the oxygen concentration modification step, in this situation, will take into consideration the sum of areas A_1 and A_2 for purpose of solving equation (21), ignoring area A_3 above the baseline.

Please cancel the paragraphs beginning at page 20, line 9, and page 20, line 15, in their entirety as follows:

~~Fig. 6 illustrates that a second drop in the patient's arterial oxygen saturation will occur at time x due to the recirculation of the relatively oxygen poor blood. If this second drop, which is represented by area B_2 , is minimal, it can be ignored for purposes of determining the time period t_e to t_d . Thus, the time period t_e to t_{d2} associated with areas B_1 and B_2 are used to solve equation (21).~~

~~However, if this second drop is not minimal, the time period t_e to t_{d1} associated with area B_1 alone is used for solving equation (21). The location of time t_{d1} is determined using any conventional extrapolation technique. Of course, the present invention contemplates using suitable programming or other means for deciding when the effect of recirculation, and, hence the size of area B_2 is above the predetermined minimal threshold and must be accounted for in solving equation (21).~~

Please replace the Section title at page 21, line 1, with the following rewritten title.

~~B. Technique 2 for- Calculating Cardiac Output Based on the Slopes of
the Curves~~

Please cancel the paragraph beginning at page 17, line 17, in its entirety as follows:

~~Figs. 7 and 8, like Figs. 3 and 4, illustrate the changes in the patient's oxygen uptake and arterial oxygen saturation, respectively, resulting from the oxygen concentration~~

modification step. From Fig. 7, it can be appreciated that the change in oxygen uptake that takes place during the first breath of the oxygen concentration modification step can be defined in terms of its slope as:

$$\Delta VO_2 = \frac{\Delta y}{\Delta x} = \frac{y_2 - y_1}{x_2 - x_1} = \frac{VO_2(t_3) - VO_2(t_1)}{t_3 - t_1}, \quad (23)$$

recall from above that t_1 corresponds to the start of inspiration and that t_3 corresponds to the end of expiration, and where $VO_2(t_1)$ and $VO_2(t_3)$ are the oxygen uptakes at times t_1 and t_3 , respectively. It can be further appreciated that equation (23) defines the slope of dashed line C in Fig. 7.

Please cancel the paragraph beginning at page 21, line 13, in its entirety as follows:

From Fig. 8, it can be appreciated that that the change in fractional arterial oxygen concentration that takes place during the same time period $t_3 - t_1$ can also be defined in terms of its slope as:

$$\Delta XaO_2 = \frac{XaO_2(t_5) - XaO_2(t_4)}{t_5 - t_4}, \quad (24)$$

where, $t_5 - t_4 = t_3 - t_1$, and where $XaO_2(t_5)$ and $XaO_2(t_4)$ are the arterial oxygen concentration at times t_5 and t_4 , respectively. It can be further appreciated that equation (24) defines the slope of dashed line D in Fig. 8. Therefore, this cardiac output determination technique is referred to in the immediately preceding section heading as the "Slopes of the Curve" technique. From equation (15) it is known that:

$$\Delta V = \frac{\Delta VO_2}{\Delta XaO_2} \quad (25)$$

Substituting equations (23) and (24) in to equation (25) yields:

$$\Delta V = \left[\frac{VO_2(t_3) - VO_2(t_1)}{t_3 - t_1} \right] \left[\frac{t_5 - t_4}{XaO_2(t_5) - XaO_2(t_4)} \right] \quad (26)$$

From equations (13) and (26), the patient's cardiac output Q in liters per minute is defined as:

$$Q = \frac{\Delta V}{t_3 - t_1} = \left[\frac{VO_2(t_3) - VO_2(t_1)}{(t_3 - t_1)^2} \right] \left[\frac{t_5 - t_4}{XaO_2(t_5) - XaO_2(t_4)} \right] \quad (27)$$

Please replace the paragraph beginning at page 22, line 7, with the following rewritten paragraphs.

~~It can be appreciated that determining cardiac output based on the slopes of lines C and D is advantageous in that the effects of recirculation, if any, do not influence the determination of cardiac output.~~

In another formulation for cardiac output, we start with the simple relationship between the volume of oxygen contained in an arbitrary volume of flowing blood. The oxygen volume can be evaluated as:

$$\Delta VO_2 = (\Delta X_a O_2)(\Delta V) \quad (22)$$

If we solve for total blood volume, equation (22) becomes

$$\Delta V = \frac{\Delta VO_2}{\Delta X_a O_2} \quad (23)$$

We will assume that the volume of oxygen in the numerator of (23) is simply the oxygen taken up by the blood as measured at the airway. This is simply:

$$\Delta VO_2 = VO_2(t_{\text{start}}) - VO_2(t_{\text{end}}), \quad (24)$$

where t_{start} is the volume at an arbitrary starting point on the volume time curve of airway oxygen and t_{end} is the volume at some point in time after t_{start} .

The change in arterial oxygen concentration can then simply be written as:

$$\Delta X_{aO_2} = X_{aO_2}(t'_{\text{start}}) - X_{aO_2}(t'_{\text{end}}), \quad (25)$$

where t'_{start} is the temporal location in the concentration curve that corresponds physically to t_{start} and t'_{end} is the temporal location in the concentration curve that corresponds physically to t_{end} .

Substituting equations (24) and (25) into (23), we have

$$\Delta V = \frac{VO_2(t_{\text{start}}) - VO_2(t_{\text{end}})}{X_{aO_2}(t'_{\text{start}}) - X_{aO_2}(t'_{\text{end}})}, \quad (26)$$

Because equation (26) represents the volume of blood, we can calculate the cardiac output as:

$$CO = \frac{\Delta V}{t'_{\text{end}} - t'_{\text{start}}}, \quad (27)$$

Note that because cardiac output is the flow of blood, we must use the time span associated with the flowing blood, $t'_{\text{end}} - t'_{\text{start}}$.

Finally, substituting equation (26) into equation (27), we have:

$$CO = \left[\frac{1}{t'_{\text{end}} - t'_{\text{start}}} \right] \left[\frac{VO_2(t_{\text{start}}) - VO_2(t_{\text{end}})}{X_{aO_2}(t'_{\text{start}}) - X_{aO_2}(t'_{\text{end}})} \right]. \quad (28)$$

Referring now to Figs. 7 and 8, for example, t_{start} corresponds to point t_1 , t_{start} corresponds to point t_4 , t_{end} is arbitrarily selected for illustration purposes as t_3 , and t_{end} therefore correspond to point t_5 . Thus, cardiac output can be determined as:

$$\text{CO} = \left[\frac{1}{t_5 - t_4} \right] \left[\frac{\text{VO}_2(t_1) - \text{VO}_2(t_3)}{X_{aO_2}(t_4) - X_{aO_2}(t_5)} \right] \quad (29)$$

Please replace the paragraph beginning at page 22, line 12, with the following rewritten paragraph.

Yet another technique for determining cardiac output involves comparing the magnitude of the change in oxygen uptake with the magnitude of the change in arterial oxygen concentration resulting from the oxygen concentration modification step. Figs. 9 and 10 illustrate the changes in the patient's oxygen uptake and arterial oxygen saturation, respectively, resulting from the oxygen concentration modification step. From Fig. 9, it can be appreciated that there is a relatively large initial drop in oxygen uptake at the start of the oxygen concentration modification step, i.e., from time t_1 to t_3 . The magnitude of this drop can be determined from the output of the flow sensor and the oxygen analyzer using any conventional technique. From Fig. 10, it can be appreciated that there is a corresponding drop in arterial oxygen saturation. Although, as noted above, this drop in arterial oxygen concentration is delayed in time from the initial drop in oxygen uptake. This drop begins at time t_c and reaches a maximum difference from the initial baseline level at time t_m . The value of the fractional arterial oxygen concentration at t_m , $X_{aO_2}(t_m)$, can be determined using any conventional technique.

Please replace the paragraph beginning at page 23, line 6, with the following rewritten paragraph.

As a side note, it is worth remembering that the oxygen concentration modification step also contemplates increasing the patient's arterial oxygen in some situations. In which case, the change in oxygen uptake will be in the positive direction, opposite that shown in Figs. 3A, 3B, 5A, 5B, 7, and 9. Similarly, the change in the fractional arterial oxygen concentration will also be in the positive direction, opposite that shown in Figs. 4, 6, 8, and 10. The techniques for determining cardiac output discussed herein are equally applicable where the oxygen concentration modification step is performed by increasing the patient's arterial oxygen.

Please replace the paragraph beginning at page 23, line 14, with the following rewritten paragraph.

Referring again to Figs. 9 and 10, one embodiment of the present invention contemplates comparing the magnitude of the change in oxygen uptake from time t_1 to t_3 with the magnitude of the change in arterial oxygen concentration from time t_c to t_m , so that the patient's cardiac output is defined as:

$$CO = \frac{\Delta \dot{V}O_2 (\text{Magnitude } t_1 \text{ to } t_3)}{\Delta XaO_2 (\text{Magnitude } t_c \text{ to } t_m)} = \frac{\dot{V}O_2 (\text{Magnitude } t_1 \text{ to } t_3)}{\Delta XaO_2 (\text{Magnitude } t_c \text{ to } t_m)} \quad (2830)$$

It can be appreciated that equation (2830) represents a direct calculation for cardiac output because the units represented by the numerator are, for example, liters/second or liters/minute, and the denominator is unitless.

Please replace the paragraph beginning at page 24, line 1, with the following rewritten paragraph.

Another embodiment of the present invention contemplates determining cardiac output based on the time period t_c to t_e , where t_c to $t_e = t_1$ to t_3 , so that

$$CO = \frac{\Delta \dot{V}O_2 (\text{Magnitude } t_1 \text{ to } t_3)}{\Delta X_{aO_2} (\text{Magnitude } t_c \text{ to } t_e)} = \frac{\Delta \dot{V}O_2 (\text{Magnitude } t_1 \text{ to } t_3)}{\Delta X_{aO_2} (\text{Magnitude } t_c \text{ to } t_e)} \quad (2931)$$

As with equation (2830), equation (2931) also represents a direct calculation for cardiac output because the units represented by the numerator are, for example, liters/second or liters/minute, and the denominator is unitless. In these embodiments, the change in magnitude of the oxygen uptake and fractional arterial oxygen concentration are monitored during the oxygen modification step, which is why this technique is referred to in the preceding section heading as the “Magnitude of the Curve” technique.

The determination of cardiac output using equations (30) or (31) can also be understood by referring back to equation (16). That is, equation (16) can be readily derived to arrive at equation (30) or (31). For example, if equation (16) is adjusted by multiplying the denominator across the expression we have:

$$CO \int_0^T [X_{aO_2}(0) - X_{aO_2}(t)] dt = \int_0^T [\dot{V}O_{2(\text{baseline})}(0) - \dot{V}O_{2(\text{bolus})}(t)] dt \quad (32)$$

Differentiating both sides of equation (32) with respect to time yields the following expression:

$$CO[X_{aO_2}(0) - X_{aO_2}(t)] = [\dot{V}O_{2(\text{baseline})}(0) - \dot{V}O_{2(\text{bolus})}(t)] \quad (33)$$

which can be rewritten as:

$$CO = \frac{[\dot{V}O_{2(\text{baseline})}(0) - \dot{V}O_{2(\text{bolus})}(t)]}{[X_{aO_2}(0) - X_{aO_2}(t)]} \quad (34)$$

It can be appreciated that equation (34) corresponds to equations (30) and (31), where $\Delta \dot{V}O_2$ in equation (30) or (31) is equal to the expression $\dot{V}O_{2(\text{baseline})}(0) - \dot{V}O_{2(\text{bolus})}(t)$ in equation (34), and

where ΔX_{aO_2} in equations (30) and (31) is equal to the expression $X_{aO_2}(0) - X_{aO_2}(t)$ in equation (34), except that specific times t_m or t_c are used in equations (30) and (31) in place of $\dot{V}O_{2(bolus)}(t)$ in equation (34).

The Section entitled, "D. Technique 4 - Calculating Cardiac Output Based on the Volume of the Blood Flow" should be deleted in its entirety as follows:

~~D. Technique 4 - Calculating Cardiac Output Based on the Volume of
Blood Flow~~

~~It is known that the volume of blood flowing through the heart during a breathing cycle is defined as:~~

$$\text{V}_{\text{blood}} = \int_{t_1}^{t_2} \frac{\Delta \dot{V}O_2}{\Delta X_{aO_2}} dt. \quad (30)$$

~~and the flow of blood, i.e., cardiac output, in liters per minute, for example, is defined as:~~

$$Q_{\text{blood}} = \frac{V_{\text{blood}}}{t}. \quad (31)$$

~~It can be appreciated that equation (30) can be substituted into equation (31) to determine the cardiac output.~~

Please replace the paragraph beginning at page 27, line 5, with the following rewritten paragraph.

However, the present invention also contemplates that the patient flow measuring system, the oxygen analyzing system, and arterial oxygen concentration measuring system, or any

combination thereof, can be integrated into a single housing 43, as shown, for example, in Fig. 12. In this embodiment, the measuring elements of each system, such as the flow element 33, the airway adapter and O₂ transducer 35, and the pulse oximeter sensor 39, provide inputs, e.g., electronic, optical, pneumatic, or otherwise, to one or more processing systems in housing 43.

Please replace the paragraph beginning at page 27, line 12, with the following rewritten paragraph.

Also necessary for purposes of the present invention, as shown in Fig. 12, is a device or technique, generally indicated at 50, for inducing a change in the patient's arterial oxygen concentration. In the illustrated exemplary embodiment, device 50 is a rebreathing system that captures the patient's expired gas in a collection reservoir 52. A valve 54 controls the flow of gas, so that when the cardiac output system is not actuated, the patient's airway communicates with ambient atmosphere or a conventional ventilator or pressure support system (not shown). In this embodiment, when the cardiac output is to be measured, valve 54 is controlled manually or via processor 36, to cause the patient's exhaled gas ~~passed~~to be delivered to reservoir 52 where it is collected. Because the gas collected in reservoir 52 has been exhaled by the patient, its oxygen concentration is significantly reduced.

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AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings includes changes to FIGS. 3-8 . These sheets, which include, FIGS. 3A-8, replace the original sheets including FIGS. 3-8.

Attachment: Replacement Sheets.